GENITOURINARY
MEDICINE

Editorial

Multidrug resistant tuberculosis: practical lessons for HIV units

The emergence of drug resistant and multidrug resistant (MDR) tuberculosis has been well documented in the United States and other parts of the world. Since 1990, at least ten nosocomial outbreaks of MDR tuberculosis have been reported in the United States and Europe,[1-5] including two recent outbreaks in London.[6-7] Most of those who developed tuberculosis in these outbreaks were HIV-infected patients, although transmission and active disease have also been documented in immunocompetent health care workers.[1] Two recent studies based on restriction-fragment length polymorphisms have suggested that recent transmission accounts for as much as 40% of drug resistant adult cases, particularly among HIV infected persons.[8 9] Factors identified as contributing to these outbreaks included a failure or delay in the recognition and diagnosis of tuberculosis, delayed laboratory identification of drug-resistance and thus initiation of appropriate treatment, failure to achieve and maintain effective isolation of known or suspected tuberculosis cases, and inadequate ventilation in the ward or areas where procedures leading to aerosolisation of sputum are performed.[10]

Initial follow-up studies of patients with MDR tuberculosis and HIV infection reported extremely high mortality rates, particularly among patients with AIDS. Survival data showed a median survival of 4 to 16 weeks for patients with MDR-tuberculosis and AIDS,[11] and 14 months for HIV infected patients without a diagnosis of AIDS.[12] More recent studies have observed improved outcomes when HIV infected patients received prompt diagnosis and treatment with two or more drugs that had *in vitro* activity against the drug-resistant isolates. However, only a small percentage of patients with MDR-tuberculosis achieve a sustained sputum culture conversion to negative, and many remain intermittently smear and culture positive for some time, despite clinical signs of response.[11]

An important source of the delay in diagnosis is the difficulty in recognizing tuberculosis in patients with HIV infection. Such patients are more likely to present atypically, with, for example, meningitis, skin lesions, bacteraemia, or features of primary disease.[12] The presenting signs and symptoms also tend to be non-specific, and may be confused with *Mycobacterum avium intracellulare* infection, lymphoma, AIDS wasting syndrome, cytomegalovirus infection, or other opportunistic diseases. The clinical presentation of patients with drug-susceptible and MDR tuberculosis tend to be similar, although one report found that those with MDR tuberculosis were more likely to have both pulmonary and extrapulmonary disease.[11] There is no evidence that MDR strains are more infectious than drug-susceptible ones.

In contrast to the well-established treatment protocols for drug-susceptible tuberculosis, the optimal therapy for drug-resistant and MDR tuberculosis is neither well studied nor standardised. It is generally recommended that patients should receive at least three, and usually four drugs to which the current isolate is susceptible, and which the patient has not received in the past. The list of candidate drugs used to treat MDR tuberculosis and the most common side effects are shown in the table. The selection of specific empirical regimens will depend on the local pattern of drug susceptibility, since resistance patterns may vary from country to country and from hospital to hospital.[13] For example, the organism isolated in the 1995 outbreak in London was resistant to isoniazid, rifampicin, pyrizinamide, clofazimine and ethionamide, and sensitive to streptomycin, ciprofloxacin, ethambutol, clarithromycin, amikacin and doxycline.[6] While the isolate in the 1996 outbreak in a nearby hospital was resistant to rifampicin, rifabutin, pyrizinamide, clofazimine, ciprofloxacin, and clarithromycin.[7] Patients generally require hospitalisation for the initiation of therapy, primarily to monitor for toxicity, malabsorption of drugs and tolerance of medication. In general, it is recommended that patients with MDR tuberculosis should be treated for at least two years.[13]

Another factor that has contributed significantly to recent outbreaks of MDR tuberculosis is the slow turn-around time for obtaining laboratory confirmation of infection and data on drug susceptibility. In the past, the physician has had to rely on diagnostic methods, such as acid-fast stain and culture that required 4 to 6 weeks, with an additional 2 to 4 weeks for data on drug susceptibility. However, new rapid laboratory methods offer the potential to dramatically reduce the time to diagnosis of infection. The automated BACTEC system has been shown to identify mycobacteria in two weeks, with an additional 4 to 7 days for drug susceptibility testing.[14] Amplification methods and genetic probes aid in rapidly detecting and differentiating *M tuberculosis* from other mycobacterial species.[15] However, these new techniques require greatly increased resources and expertise which may not be available in a number of clinical laboratories.

Side effects of second line anti-tuberculous therapies

Drug	Reaction
Aminoglycosides, such as amikacin, streptomycin and kanamycin	Ototoxicity, nephrotoxicity
Quinolones, such as, ciprofloxacin, ofloxacin	Nausea, abdominal pain, tremulousness
Ethionamide	Metallic taste, abdominal pain, hepatoxicity, hyperuricaemia
Cycloserine	Depression, seizures, psychosis
Clofazimine	Skin and body fluid discolouration, abdominal pain
Para-aminosalicylate	Nausea, abdominal pain, rash

Because of the increasing threat of nosocomial tuberculosis to both patients and health care workers, there is a clear need for each HIV unit to develop or adopt published guidelines for the control and prevention of tuberculosis transmission, and MDR tuberculosis in particular. Guidelines for the prevention of transmission of tuberculosis have been published in the United States,[16] and are currently being updated in the UK under the auspices of the Department of Health. The extent of the control measures adopted by any one unit will depend on the severity of the problem posed by tuberculosis in that particular setting.

At a minimum, there should be an emphasis in all units on early detection, isolation and treatment of infectious tuberculosis. HIV physicians and nurses should be educated to maintain a high index of suspicion for tuberculosis and drug-resistant tuberculosis, and to "think tuberculosis" when any patient presents with cough and fever, regardless of their radiographic findings. Any HIV positive patient with respiratory symptoms and/or abnormal chest radiographs should be routinely placed in isolation until tuberculosis has been excluded. Patients should only be discharged when they are no longer infectious or when arrangements have been made for appropriate isolation from contact with susceptible individuals. All cases of proven infectious tuberculosis should be followed closely to ensure that patients are taking their medications. If a lack of compliance is suspected then directly observed therapy should be employed. Laboratory studies should also be conducted as soon as possible to confirm or exclude the presence of tuberculosis. Specimens for acid-fast-bacilli should be examined on the same day that the samples arrive at the laboratory, and where there is a high prevalence of tuberculosis, laboratories should have rapid methods for culture and sensitivity testing available.

The adoption of these infection control practices in several well-characterised outbreaks, namely heightened suspicion of tuberculosis, strict isolation of infected patients, and extra laboratory resources appeared to be the most important factors contributing to the successful control of the outbreak.

Supplemental measures include the use of environmental controls, such as augmented ventilation, use of germicidal UV light and high-efficiency air filtration (HEPA) and masks. The controversy over these measures has been based largely on the lack of efficacy data and their prohibitive costs.

Various studies have shown that the introduction of fresh air into an environment can dilute the concentration of infectious particles and reduce the probability of tuberculosis transmission. One air exchange (that is, the amount of air required to completely replace an entire room's air volume) removes approximately 67% of air contaminants. Current US recommendations advocate at least 6 air exchanges per hour for isolation rooms and treatment rooms used for high-risk procedures involving aerosolisation of sputum.[16] An isolation room of a patient with tuberculosis also needs to be under negative pressure to prevent the escape of organisms from the room to the corridor. The use of germicidal UV light and high-efficiency air filtration (HEPA), which is capable of filtering AFB from the air, may be necessary when adequate ventilation is not feasible, although neither of these approaches have been strongly advocated in the UK.

The use of face masks also remains controversial. The size of the aerosol droplet nuclei known to be infectious in animal models is 1 to 5 microns, and for this reason it has been recommended in the United States that disposable dust mist fume respiratory masks or the HEPA-filter containing mask rather than simple surgical masks are used.[16] There is ongoing discussion about the relative efficacy of the available masks, but, because transmission has been documented at significant distances from the isolation rooms, use of masks by staff only while in direct contact with tuberculosis cases is insufficient. However, their use is recommended for those health care workers experiencing the greatest risk of exposure in high risk environments, such as bronchoscopy suites, aerosol treatment or sputum induction areas.

In summary, rapid recognition of cases of tuberculosis and their effective isolation should be the priority infection control measure in HIV units. Less clear are the data for engineering controls and the requirements for mask use, but further guidance will be offered on these issues in the forthcoming Department of Health guidelines for the prevention of nosocomial transmission of tuberculosis. Individual units should assess their level of tuberculosis transmission and base their adoption of the suggested control measures on this evaluation.

PHILIPPA EASTERBROOK
Chelsea and Westminster Hospital,
London SW10 9NH, UK

1 Nosocomial transmission of multidrug resistant tuberculosis among HIV-infected persons—Florida and New York, 1988–1991. *MMWR* 1991;40: 585–91.
2 Edlin BR, Tokars JI, Grieco MH, Crawford JT, Williams J, Sordillo EM, *et al.* An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992;326:1514–21.
3 Fischl MA, Uttamhandani RB, Daikos GL, Poblete RB, Moreno JN, Reyes RR, *et al.* An outbreak of tuberculosis caused by multiple drug-resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med* 1992;117:177–83.
4 Pearson ML, Jareb JA, Crawford JT, Davis BJ, Dooley SW, Jarvis WR. Nosocomial transmission of multi-drug resistant Mycobacterium tuberculosis. *Ann Intern Med* 1992;117:191–6.
5 Multidrug resistant tuberculosis outbreak on an HIV ward—Madrid, Spain, 1991–1995. *MMWR* 1996;45:330–23.
6 Outbreak of hospital acquired multidrug resistant tuberculosis. *CDR* 1995; 5(34):161.
7 Multidrug resistant tuberculosis in a London hospital. *CDR* 1996;6(24): 205.
8 Alland D, Kalkut GE, Moss AR, McAdam RA, Hahn JA, Bosworth W, *et al.* Transmission of tuberculosis in New York City: an analysis by DNA fingerprinting and conventional epidemiologic methods. *N Engl J Med* 1994;330:1710–6.
9 Small PM, Hopewell PC, Singh SP, Paz A, Parsonnet J, Ruston DC, *et al.* The epidemiology of tuberculosis in San Francisco: a population-based study using conventional and molecular methods. *N Engl J Med* 1994; 330:1703–9.
10 Jarvis WR. Nosocomial transmission of multi-drug resistant *Mycobacterium tuberculosis. Am J Infect Control* 1995;23:146–51.
11 Fischl MA, Daikos GL, Uttamchandani RB, Poblete RB, Moreno JN, Reyes RR, *et al.* Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple drug-resistant bacilli. *Ann Intern Med* 1992;117:184–90.
12 Mathur P, Sacks L, Auten G, Sall R, Levy C, Gordin F. Delayed diagnosis of pulmonary tuberculosis in city hospitals. *Arch Intern Med* 1994;154: 306–10.
13 Iseman MD. Treatment of multidrug resistant tuberculosis. *N Engl J Med* 1993;329:784–91.
14 Roberts GD, Goodman NL, Heifets L, Larsh HW, Linder TH, McClatchy JK, *et al.* Evaluation of the BACTEC radiometric method for recovery of mycobacteria and drug susceptibility testing of *Mycobacterium tuberculosis* from acid-fast smear positive specimens. *J Clin Microbiol* 1983;18: 689–96.
15 Vuorinen P, Miettinen A, Vuento R, Hallstrom O. Direct detection of *Mycobacterium tuberculosis* in respiratory specimens by Gen-probe amplified *Mycobacterium tuberculosis* direct test and Roche Amplicor *Mycobacterium tuberculosis* test. *J Clin Microbiol* 1995;33:1856–59.
16 Centers for Disease Control. Guidelines for preventing the transmission of tuberculosis in health care settings, with special focus on HIV-related issues. *MMWR* 1990;39:1–29.